
CRISPR Screening of CAR T Cells and Cancer Stem Cells Reveals Critical Dependencies for Cell-Based Therapies.

Journal: Cancer Discov

Publication Year: 2021

Authors: Dongrui Wang, Briana C Prager, Ryan C Gimple, Brenda Aguilar, Darya Alizadeh, Hongzhen Tang, Deguan Lv, Renate Starr, Alfonso Brito, Qiulian Wu, Leo J Y Kim, Zhixin Qiu, Peng Lin, Michael H Lorenzini, Behnam Badie, Stephen J Forman, Qi Xie, Christine E Brown, Jeremy N Rich

PubMed link: 33328215

Funding Grants: Phase I Study of Chimeric Antigen Receptor Engineered Central Memory T cells for the Treatment of Malignant Glioma

Public Summary:

Glioblastoma (GBM) contains self-renewing GBM stem cells (GSC) potentially amenable to immunologic targeting, but chimeric antigen receptor (CAR) T-cell therapy has demonstrated limited clinical responses in GBM. Here, we interrogated molecular determinants of CAR-mediated GBM killing through whole-genome CRISPR screens in both CAR T cells and patient-derived GSCs. Screening of CAR T cells identified dependencies for effector functions, including TLE4 and IKZF2. Targeted knockout of these genes enhanced CAR antitumor efficacy. Bulk and single-cell RNA sequencing of edited CAR T cells revealed transcriptional profiles of superior effector function and inhibited exhaustion responses. Reciprocal screening of GSCs identified genes essential for susceptibility to CAR-mediated killing, including RELA and NPLOC4, the knockout of which altered tumor-immune signaling and increased responsiveness of CAR therapy. Overall, CRISPR screening of CAR T cells and GSCs discovered avenues for enhancing CAR therapeutic efficacy against GBM, with the potential to be extended to other solid tumors. SIGNIFICANCE: Reciprocal CRISPR screening identified genes in both CAR T cells and tumor cells regulating the potency of CAR T-cell cytotoxicity, informing molecular targeting strategies to potentiate CAR T-cell antitumor efficacy and elucidate genetic modifications of tumor cells in combination with CAR T cells to advance immuno-oncotherapy.

Scientific Abstract:

Glioblastoma (GBM) contains self-renewing GBM stem cells (GSC) potentially amenable to immunologic targeting, but chimeric antigen receptor (CAR) T-cell therapy has demonstrated limited clinical responses in GBM. Here, we interrogated molecular determinants of CAR-mediated GBM killing through whole-genome CRISPR screens in both CAR T cells and patient-derived GSCs. Screening of CAR T cells identified dependencies for effector functions, including TLE4 and IKZF2. Targeted knockout of these genes enhanced CAR antitumor efficacy. Bulk and single-cell RNA sequencing of edited CAR T cells revealed transcriptional profiles of superior effector function and inhibited exhaustion responses. Reciprocal screening of GSCs identified genes essential for susceptibility to CAR-mediated killing, including RELA and NPLOC4, the knockout of which altered tumor-immune signaling and increased responsiveness of CAR therapy. Overall, CRISPR screening of CAR T cells and GSCs discovered avenues for enhancing CAR therapeutic efficacy against GBM, with the potential to be extended to other solid tumors. SIGNIFICANCE: Reciprocal CRISPR screening identified genes in both CAR T cells and tumor cells regulating the potency of CAR T-cell cytotoxicity, informing molecular targeting strategies to potentiate CAR T-cell antitumor efficacy and elucidate genetic modifications of tumor cells in combination with CAR T cells to advance immuno-oncotherapy. This article is highlighted in the In This Issue feature, p. 995.

Source URL: <https://www.cirm.ca.gov/about-cirm/publications/crispr-screening-car-t-cells-and-cancer-stem-cells-reveals-critical>